Labeling Guidance
Revised 2/92

CARBIDOPA AND LEVODOPA TABLETS USP

DESCRIPTION

When carbidopa and levodopa tablets are to be given to patients who are being treated with levodopa, levodopa must be discontinued at least eight hours before therapy with the combination product is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS and DOSAGE AND ADMINISTRATION sections before initiating therapy.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.25. It is designated chemically as (-)-L-α-hydrazino-α-methyl-ß-(3,4-dihydroxybenzene)-propanoic acid monohydrate. It has the following structural formula:

Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.23.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.19. It is designated chemically as (-)-L-α-amino-ß-(3,4-dihydroxybenzene) propanoic acid. It has the following structural formula:

Carbidopa and levodopa tablets for oral administration are supplied in the following strengths _____.

Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).

CLINICAL PHARMACOLOGY

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

When levodopa is administered orally it is rapidly converted to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. In dogs, reduced formation of dopamine in extracerebral tissues, such as the heart, provides protection against the development of dopamine-induced cardiac arrhythmias. Clinical studies tend to support the hypothesis of a similar protective effect in humans although controlled data are too limited at the present time to draw firm conclusions.

Carbidopa reduces the amount of levodopa required by about 75 percent and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa

in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

INDICATIONS AND USAGE

Carbidopa and levodopa tablets are indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication. This product is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

The incidence of levodopa-induced nausea and vomiting is less with this combination product than with levodopa. In many patients this reduction in nausea and vomiting will permit more rapid dosage titration.

In some patients a somewhat smoother antiparkinsonian effect results from therapy with carbidopa and levodopa than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from carbidopa and levodopa therapy.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, carbidopa and levodopa can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. *Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at lower*

dosages and sooner during therapy with carbidopa and levodopa than with levodopa.

Certain patients who responded poorly to levodopa have improved when carbidopa and levodopa was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give this combination product to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing carbidopa and levodopa with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS

Monoamine oxidase inhibitors and carbidopa and levodopa should not be given concomitantly. These inhibitors must be discontinued at least two weeks prior to initiating therapy with this combination product.

Carbidopa and levodopa is contraindicated in patients with known hypersensitivity to this drug, and in narrow angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When patients are receiving levodopa, it must be discontinued at least eight hours before therapy with the combination product is started. Carbidopa and levodopa should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION). Patients who are taking this combination product should be instructed not to take additional levodopa unless it is prescribed by the physician.

As with levodopa, the combination product may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with carbidopa and levodopa than with levodopa.* The occurrence of dyskinesias may require dosage reduction.

Carbidopa and levodopa should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Care should be exercised in administering the combination product, as with levodopa, to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa there is a possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of carbidopa and levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage In Pregnancy And Lactation: Although the effects of carbidopa and levodopa on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of carbidopa and levodopa in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child. This product should not be given to nursing mothers.

Usage In Children: The safety of carbidopa and levodopa tablets in patients under 18 years of age has not been established.

PRECAUTIONS

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide angle glaucoma may be treated cautiously with carbidopa and levodopa provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of this combination product than with levodopa.

Carbidopa and levodopa may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with carbidopa and levodopa.

Symptomatic postural hypotension can occur when carbidopa and levodopa is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when carbidopa and levodopa therapy is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants with carbidopa and levodopa.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with carbidopa and levodopa should be carefully observed for loss of therapeutic response.

ADVERSE REACTIONS

The most common serious adverse reactions occurring with carbidopa and levodopa therapy are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with carbidopa and levodopa has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, gastrointestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.
Other adverse reactions that have been reported with levodopa are:

Nervous System: ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.

Psychiatric: confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.

Gastrointestinal: dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue.

Metabolic: weight gain or loss, edema.

Integumentary: malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair.

Genitourinary: urinary retention, urinary incontinence, dark urine, priapism.

Special Senses: diplopia, blurred vision, dilated pupils, oculogyric crises.

Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE

Management of acute overdosage with carbidopa and levodopa is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of this product.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as carbidopa and levodopa tablets should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

DOSAGE AND ADMINISTRATION

The optimum daily dosage of carbidopa and levodopa must be determined by careful titration in each patient. Carbidopa and levodopa tablets are available in a 1:4 ratio of carbidopa to levodopa (25 mg/100 mg) as well as 1:10 ratio (25 mg/250 mg and 10 mg/100 mg). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Usual Initial Dosage
Dosage is best initiated with one tablet of carbidopa and levodopa 25 mg/100 mg three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of carbidopa and levodopa 25 mg/100 mg a day is reached.

If carbidopa and levodopa 10 mg/100 mg is used, dosage may be initiated with one tablet three or four times a day. However, this will not provide an adequate amount of carbidopa for many patients. Dosage may be increased by one tablet every day or every other day until a total of eight tablets (2 tablets q.i.d.) is reached.

How To Transfer Patients From Levodopa
Levodopa must be discontinued at least eight hours before starting this combination product. A daily dosage of carbidopa and levodopa should be chosen that will provide approximately 25 percent of the previous levodopa dosage. Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of carbidopa and levodopa 25 mg/100 mg three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of carbidopa and levodopa 25 mg/250 mg three or four times a day.

Maintenance
Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one 25 mg/100 mg tablet may be substituted for each 10 mg/100 mg tablet. When more levodopa is required, each 25 mg/250 mg tablet should be substituted for a 25 mg/100 mg tablet or a 10 mg/100 mg tablet. If necessary, the dosage of carbidopa and levodopa 25 mg/250 mg may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly with this combination product than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with carbidopa and levodopa than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Current evidence indicates that other standard drugs for Parkinson's disease (except levodopa) may be continued while carbidopa and levodopa is being administered, although their dosage may have to be adjusted.

If general anesthesia is required, carbidopa and levodopa may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

- Established name
- Strength of dosage form
- Package
- Dosage form, shape, color, imprinting, scoring, etc.
- Special handling and storage conditions

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